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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/591,159

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Jan Barnikov

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12/11/2009

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EXAMINER

PAK, YONG D

ART UNIT

PAPER NUMBER

1652

MAIL DATE

DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/591,159	Applicant(s) BARNIKOV ET AL.	
	Examiner YONG D. PAK	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 August 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 9-44 is/are pending in the application.
- 4a) Of the above claim(s) 15-36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 9-13 and 37-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application is 371 of PCT/EP05/50899.

The amendment filed August 28, 2009, amending claim 1, canceling claims 2-7, and adding claims 38-44, has been entered. No new matter has been entered.

Claims 1 and 9-44 are pending. Claims 15-36 are withdrawn. Claims 1-7, 9-14, and 37-44 are under consideration.

Election/Restrictions

Applicant's election of Group I (claims 1-7, 9-30, and 37) with a further species election of the mutant human AGT consisting of the following modifications and properties:

Lys32Ile, Leu33Phe, Cys62Ala, Gin 115 Ser, Gin 116His, Lys 125Ala, Ala127Thr, Arg128Ala, Gly131Lys, Gly132Thr, Met134Leu, Arg135Ser, Cysl50G1y, Serl51G1y, Ser152Asp, Ala154Asp, Asn157Gly, Ser159Glu, truncation at 182

- (a) no detectable DNA interaction;
- (b) localization of the expressed protein in eukaryotic cells that is no longer restricted to the nucleus;
- (c) at least 1 O-fold improved expression yield as soluble protein and improved stability in E. coli;
- (d) improved stability under oxidizing conditions;

- (e) at least six-fold improved stability within cells after reaction with a substrate;
- (f) improved stability outside cells before and after reaction with a substrate; (g) at least four-fold increased in vitro solubility;
- (h) 45-fold higher reactivity against O6-alkylguanine substrates;
- (i) no detectable reactivity against DNA-based substrates; and
- (j) at least 10-fold reduced reactivity against Ng-substituted O6-alkylguanine substrates

in the reply filed on January 30, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 15-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention/species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on January 30, 2009.

Examiner notes that claims 16, 17, 19, 20, and 24 do not read on the elected species because the mutant of claims 16-17 and 19-20 does not have a Gly at position 150 and the mutant of claim 24 has a deletion of Leu34.

Examiner also notes that claims 9-14 are drawn to non-elected species. Only those encompassed by the elected species will be examined.

Applicants argue that claims 16-17, 19, and 24 read on the elected species because the limitation "and optionally 1 to .. additional amino acid modifications" encompasses Asn150Gly substitution. Examiner respectfully disagrees. Claims 16-17, 19, and 24 are drawn to AGT mutants which must have a Cys150Asn substitution and the elected species has a Cys150Gly substitution. Further, claims 16-17, 19, and 24 do not recite a limitation that the AGT mutant has a Asn150Gly substitution. Therefore, withdrawal of claims 16-17, 19 and 24 is maintained.

Response to Arguments

Applicant's amendment and arguments filed on August 28, 2009, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied.

Claim Rejections - 35 USC § 101

In view of the amendment of claim 1 and cancellation of claims 2-7, the rejection of claims 1-7 and 9-14 under 35 U.S.C. 101, as being drawn to non-statutory subject matter has been **withdrawn**.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In view of the amendment of claim 1 and cancellation of claims 2-7, the rejection of claims 1-7 and 9-14 under 35 U.S.C. 112, 2nd paragraph, as being indefinite has been **withdrawn**.

Claim 1 and claims 9-14 and 37-44 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 recite the phrase "wild type human AGT having the amino acid sequence of SEQ ID NO:1". The metes and bounds of the above phrases are not clear in the context of the claims. SEQ ID NO:1 is a sequence identifier of a polynucleotide sequence. Therefore, it is unclear from the specification or from the claim as to what applicants mean by the above phrase. Clarification is requested.

Claim Rejections - 35 USC § 102

In view of the amendment of claim 1 and cancellation of claims 2-5, the rejection of claims 1-5, 9-13, and 37 under 35 U.S.C. 102(b), as being anticipated by Juillerat et al. (Chemistry & Biology Vol. 10, 2003 – form PTO-1449) has been **withdrawn** because Juillerat et al. does not teach a mutant human AGT having at least six amino acid substitutions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 9-13, and 37-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Juillerat et al. and Xu-Welliver et al.

Claims 1-5, 9-13, and 37-44 are drawn to a fusion protein comprising a mutant of a wildtype human AGT, wherein said mutant has at least six amino acid substitutions, including Pro140Phe, Asn157Arg, and Ser159Glu substitutions, wherein said fusion protein has (1) localization of the expressed mutant in eukaryotic cells that is no longer restricted to the nucleus, (2) improved expression yield or fivefold expression yield as

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soluble protein and improved stability in various host, such as *E. coli*, and (3) improved reactivity against O⁶-alkylguanine substrates.

Juillerat et al. (Chemistry & Biology Vol. 10, 2003 – form PTO-1449) discloses a fusion protein comprising a mutant of a wildtype human AGT fused to a GST protein, wherein said mutant AGT has Pro140Phe, Asn157Arg, and Ser159Glu substitutions (Table 1 on page 2). Examiner takes the position that the protein of Juillerat et al. inherently possesses the same material structure and functional characteristics as the enzyme of the instant invention since the protein of Juillerat et al. is (1) not restricted to the nucleus (page 3, right column), (2) fusion to the GST protein affords stability/solubility to the AGT mutant, (3) has improved reactivity against O⁶-alkylguanine substrates (Table 1), and (4) the Office does not have facilities for examining and comparing applicant's enzyme with the enzyme of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the fusion protein comprising the mutant AGT of the prior art does not possess the same material structure and functional characteristics of the claimed fusion protein comprising the mutant AGT). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

The difference between the above references and the instant invention is that the references do not teach a mutant human AGT having at least 6 amino acid substitutions.

Xu-Welliver et al. (Biochem J. 2000 Apr 15;347(Pt 2):519-26 – form PTO-1449) discloses many O⁶-benzylguanine (BG) resistant human AGT mutants at positions 150-

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157, 159-162, 167, 169, 170, and 173 (Tables 2-3 on page 522). Xu-Welliver et al. also discloses that any amino acid substitution at position Pro140 renders the AGT resistant to BG (pages 519-520). Xu-Welliver et al. also discloses that numerous amino acid substitutions affect the ability of human AGT to accept BG at the active site without impairing the activity of said AGT (page 520).

Regarding claims 38-44, Examiner takes the position that the properties recited in claims 38-44 would necessarily flow from a mutant having six amino acid substitutions, including Pro140Phe, Asn157Arg, and Ser159Glu substitutions.

Therefore, combining the teachings of Juillerat et al. and Xu-Welliver, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to further modify the mutant AGT of Juillerat et al. with amino acid substitutions that render human AGT resistant to BG, as taught by Xu-Welliver et al.

One of ordinary skill in the art would have been motivated to combine the above references in order to further increase the resistance to BG of the mutant AGT of Juillerat et al. and/or determine if combination of amino acid substitution(s) have a synergistic effect on the resistance against BG.

One of ordinary skill in the art would have had a reasonable expectation of success site-mutagenesis is routine in the art and Xu-Welliver et al. teaches that numerous amino acid substitutions affect the ability of human AGT to accept BG at the active site without impairing the activity of said AG.

Therefore, the above references render claims 1-5, 9-13, and 37-44 *prima facie* obvious.

Examiner Comments

Examiner notes that the elected species, as outlined above on page 2, is free of prior art. Therefore, examination of other withdrawn species of the Markush-type claim was extended. Since prior art was found that anticipates the Markush-type claim with respect to a *nonelected species*, the Markush-type claim was rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated by the prior art, the amended Markush-type claim will be reexamined.

Conclusion

Claims 1-5, 9-13, and 37-44 are rejected.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Yong D Pak/
Primary Examiner, Art Unit 1652

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